



TGFb+MMP+ifn b Sequence

10	20	30	40	50	60	
1234567890	1234567890	1234567890	1234567890	1234567890	1234567890	
ATGCCGCCCT	CCGGGCTGCG	GCTGCTGCCG	CTGCTGCTAC	CGCTGCTGTG	GCTACTGGTG	60
MetProProS	erGlyLeuAr	gLeuLeuPro	LeuLeuLeuP	roLeuLeuTr	pLeuLeuVal	
CTGACGCCTG	GCCCGCCGGC	CGCGGGACTA	TCCACCTGCA	AGACTATCGA	CATGGAGCTG	120
LeuThrProG	lyProProAl	aAlaGlyLeu	SerThrCysL	ysThrIleAs	pMetGluLeu	
GTGAAGCGGA	AGCGCATCGA	GGCCATCCGC	GGCCAGATCC	TGTCCAAGCT	GCGGCTCGCC	180
ValLysArgL	ysArgIleGl	uAlaIleArg	GlyGlnIleL	euSerLysLe	uArgLeuAla	
AGCCCCCGGA	GCCAGGGGGA	GGTGCCGCCC	GGCCCGCTGC	CCGAGGCCGT	GCTCGCCCTG	240
SerProProS	erGlnGlyGl	uValProPro	GlyProLeuP	roGluAlaVa	lLeuAlaLeu	
TACAACAGCA	CCCGCGACCG	GGTGGCCGGG	GAGAGTGCAG	AACCGGAGCC	CGAGCCTGAG	300
TyrAsnSerT	hrArgAspAr	gValAlaGly	GluSerAlaG	luProGluPr	oGluProGlu	
GCCGACTACT	ACGCCAAGGA	GGTCACCCGC	GTGCTAATGG	TGGAAACCCA	CAACGAAATC	360
AlaAspTyrT	yrAlaLysGl	uValThrArg	ValLeuMetV	alGluThrHi	sAsnGluIle	
TATGACAAGT	TCAAGCAGAG	TACACACAGC	ATATATATGT	TCTTCAACAC	ATCAGAGCTC	420
TyrAspLysP	heLysGlnSe	rThrHisSer	IleTyrMetP	hePheAsnTh	rSerGluLeu	
CGAGAAGCGG	TACCTGAACC	CGTGTTGCTC	TCCCGGGCAG	AGCTGCGTCT	GCTGAGGAGG	480
ArgGluAlaV	alProGluPr	oValLeuLeu	SerArgAlaG	luLeuArgLe	uLeuArgArg	
CTCAAGTTAA	AAGTGGAGCA	GCACGTGGAG	CTGTACCAGA	AATACAGCAA	CAATTCCTGG	540
LeuLysLeuL	ysValGluGl	nHisValGlu	LeuTyrGlnL	ysTyrSerAs	nAsnSerTrp	
CGATACCTCA	GCAACCGGCT	GCTGGCACCC	AGCGACTCGC	CAGAGTGGTT	ATCTTTTGAT	600
ArgTyrLeuS	erAsnArgLe	uLeuAlaPro	SerAspSerP	roGluTrpLe	uSerPheAsp	
GTCACCGGAG	TTGTGCGGCA	GTGGTTGAGC	CGTGGAGGGG	AAATTGAGGG	CTTTCGCCTT	660
ValThrGlyV	alValArgGl	nTrpLeuSer	ArgGlyGlyG	luIleGluGl	yPheArgLeu	
AGCGCCCACT	GCTCCTGTGA	CAGCAGGGAT	AACACACTGC	AAGTGGACAT	CAACGGGTTC	720
SerAlaHisC	ysSerCysAs	pSerArgAsp	AsnThrLeuG	lnValAspIl	eAsnGlyPhe	

FIG. 1A



ACTACCGGCC	GCCGAGGTGA	CCTGGCCACC	ATTCATGGCA	TGAACCGGCC	TTTCCTGCTT	780
ThrThrGlyA	rgArgGlyAs	pLeuAlaThr	IleHisGlyM	etAsnArgPr	oPheLeuLeu	
CTCATGGCCA	CCCCGCTGGA	GAGGGCCAG	CATCTGCAA	GCGAATTCGG	GGGAGGCGGA	840
LeuMetAlaT	hrProLeuGl	uArgAlaGln	HisLeuGlnS	erGluPheGl	yGlyGlyGly	
TCCCCGCTCG	GGCTTTGGGC	GGGAGGGGGC	TCA	GCGGCCG	CAATCAACTA	900
SerProLeuG	lyLeuTrpAl	aGlyGlyGly	SerAlaAlaA	laIleAsnTy	rLysGlnLeu	
CAGCTCCAAG	AAAGGACGAA	CATTCGGAAA	TGTCAGGAGC	TCCTGGAGCA	GCTGAATGGA	960
GlnLeuGlnG	luArgThrAs	nIleArgLys	CysGlnGluL	euLeuGluGl	nLeuAsnGly	
AAGATCAACC	TCACCTACAG	GGCGGACTTC	AAGATCCCTA	TGGAGATGAC	GGAGAAGATG	1020
LysIleAsnL	euThrTyrAr	gAlaAspPhe	LysIleProM	etGluMetTh	rGluLysMet	
CAGAAGAGTT	ACACTGCCTT	TGCCATCCAA	GAGATGCTCC	AGAATGTCTT	TCTTGTCTTC	1080
GlnLysSerT	yrThrAlaPh	eAlaIleGln	GluMetLeuG	lnAsnValPh	eLeuValPhe	
AGAAACAATT	TCTCCAGCAC	TGGGTGGAAT	GAGACTATTG	TTGTACGTCT	CCTGGATGAA	1140
ArgAsnAsnP	heSerSerTh	rGlyTrpAsn	GluThrIleV	alValArgLe	uLeuAspGlu	
CTCCACCAGC	AGACAGTGTT	TCTGAAGACA	GTACTAGAGG	AAAAGCAAGA	GGAAAGATTG	1200
LeuHisGlnG	lnThrValPh	eLeuLysThr	ValLeuGluG	luLysGlnG1	uGluArgLeu	
ACGTGGGAGA	TGTCCTCAAC	TGCTCTCCAC	TTGAAGAGCT	ATTACTGGAG	GGTGCAAAGG	1260
ThrTrpGluM	etSerSerTh	rAlaLeuHis	LeuLysSerT	yrTyrTrpAr	gValGlnArg	
TACCTTAAAC	TCATGAAGTA	CAACAGCTAC	GCCTGGATGG	TGGTCCGAGC	AGAGATCTTC	1320
TyrLeuLysL	euMetLysTy	rAsnSerTyr	AlaTrpMetV	alValArgAl	aGluIlePhe	
AGGAACTTTC	TCATCATTCG	AAGACTTACC	AGAACTTCC	AAAAGTATC	TAGACC	1376
ArgAsnPheL	euIleIleAr	gArgLeuThr	ArgAsnPheG	lnAsn***Se	rArg	
				uga		

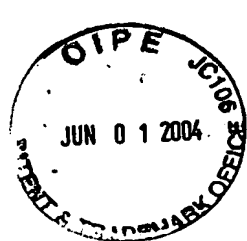
FIG. 1B



ifn+MMP+TGFB Sequence

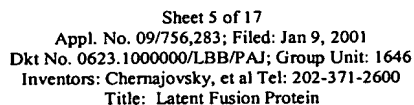
10	20	30	40	50	60	
1234567890	1234567890	1234567890	1234567890	1234567890	1234567890	
ATGAACAACA	GGTGGATCCT	CCACGCTGCG	TTCCTGCTGT	GCTTCTCCAC	CACAGCCCTG	60
MetAsnAsnA	rgTrpIleLe	uHisAlaAla	PheLeuLeuC	ysPheSerTh	rThrAlaLeu	
TCCATCAACT	ATAAGCAGCT	CCAGCTCCAA	GAAAGGACGA	ACATTCGGAA	ATGTCAGGAG	120
SerIleAsnT	yrLysGlnLe	uGlnLeuGln	GluArgThrA	snIleArgLy	sCysGlnGlu	
CTCCTGGAGC	AGCTGAATGG	AAAGATCAAC	CTCACCTACA	GGGCGGACTT	CAAGATCCCT	180
LeuLeuGluG	lnLeuAsnG	yLysIleAsn	LeuThrTyrA	rgAlaAspPh	eLysIlePro	
ATGGAGATGA	CGGAGAAGAT	GCAGAAGAGT	TACACTGCCT	TTGCCATCCA	AGAGATGCTC	240
MetGluMetT	hrGluLysMe	tGlnLysSer	TyrThrAlaP	heAlaIleG	nGluMetLeu	
CAGAATGTCT	TTCTTGTCTT	CAGAAACAAT	TTCTCCAGCA	CTGGGTGGAR	TGAGACTATT	300
GlnAsnValP	heLeuValPh	eArgAsnAsn	PheSerSerT	hrGlyTrpAs	nGluThrIle	
GTTGTACGTC	TCCTGGATGA	ACTCCACCAG	CAGACAGTGT	TTCTGAAGAC	AGTACTAGAG	360
ValValArgL	euLeuAspG	uLeuHisGln	GlnThrValP	heLeuLysTh	rValLeuGlu	
GAAAAGCAAG	AGGAAAGATT	GACGTGGGAG	ATGTCCTCAA	CTGCTCTCCA	CTTGAAGAGC	420
GluLysGlnG	luGluArgLe	uThrTrpGlu	MetSerSerT	hrAlaLeuHi	SleuLysSer	
TATTACTGGA	GGGTGCAAAG	GTACCTTAAA	CTCATGAAGT	ACAACAGCTA	CGCCTGGATG	480
TyrTyrTrpA	rgValGlnAr	gTyrLeuLys	LeuMetLysT	yrAsnSerTy	rAlaTrpMet	
GTGGTCCGAG	CAGAGATCTT	CAGGAACTTT	CTCATCATTC	GAAGACTTAC	CAGAAACTTC	540
ValValArgA	laGluIlePh	eArgAsnPhe	LeuIleIleA	rgArgLeuTh	rArgAsnPhe	
CAAAACGAAT	TG	GGGGAGG	CGGATCCCCG	CTCGGGCTTT	GGGCGGGAGG	600
GlnAsnGluP	heGlyGlyG	yGlySerPro	LeuGlyLeuT	rpAlaGlyG	yGlySerAla	
GCCGCACTAT	CCACCTGCAA	GACTATCGAC	ATGGAGCTGG	TGAAGCGGAA	GCGCATCGAG	660
AlaAlaLeuS	erThrCysLy	sThrIleASp	MetGluLeuV	aLysArgLy	sArgIleGlu	
GCCATCCGCG	GCCAGATCCT	GTCCAAGCTG	CGGCTCGCCA	GCCCCCGAG	CCAGGGGGAG	720
AlaIleArgG	lyGlnIleLe	uSerLysLeu	ArgLeuSlaS	erProProSe	rGlnGlyGlu	

FIG.2A

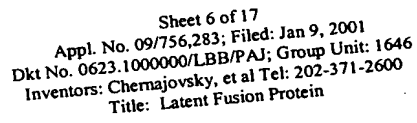


GTGCCGCCCCG	GCCCGCTGCC	CGAGGCCGTG	CTCGCCCTGT	ACAACAGCAC	CCGCGACCGG	780
ValProProG	lyProLeuPr	OGluAlaVal	LeuAlaLeuT	yrASnSerTh	rArgAspArg	
GTGGCCGGGG	AGAGTGCAGA	ACCGGAGCCC	GAGCCTGAGG	CCGACTACTA	CGCCAAGGAG	840
ValAlaGlyG	luSerAlaGl	uProGluPro	GluProGluA	laAspTyrTy	rAlaLysGlu	
GTCACCCGCG	TGCTAATGGT	GGAAACCCAC	AACGAAATCT	ATGACAAGTT	CAAGCAGAGT	900
ValThrArgV	alLeuMetVa	lGluThrHis	AsnGluIleT	yrAspLysPh	eLysGlnSer	
ACACACAGCA	TATATATGTT	CTTCAACACA	TCAGAGCTCC	GAGAAGCGGT	ACCTGAACCC	960
ThrHisSerl	leTyrMetPh	ePheAsnThr	SerGluLeuA	rgGluAlaVa	lProGluPro	
GTGTTGCTCT	CCCGGGCACA	GCTGCGTCTG	CTGAGGAGGC	TCAAGTTAAA	AGTGGAGCAG	1020
ValLeuLeuS	erArgAlaGl	uLeuArgLeu	LeuArgArgL	euHysLeuLy	sValGluGln	
CACGTGGAGC	TGTACCAGAA	ATACAGCAAC	AATTCCTGGC	GATACCTCAG	CAACCGGCTG	1080
HisValGluL	euTyrGlnLy	sTyrSerAsn	AsnSerTrPA	rgTyrheuSe	rAsnArgLeu	
CTGGCACCCA	GCGACTCGCC	AGAGTGGTTA	TCTTTTGATG	TCACCGGAGT	TGTGCGGCAG	1140
LeuAlaProS	erAspSerPr	oGluTrpLeu	SerPheAspV	alThrGlyVa	lValArgGln	
TGGTTGAGCC	GTGGAGGGGA	AATTGAGGGC	TTTCGCCTTA	GCGCCCACTG	CTCCTGTGAC	1200
TrpLeuSerA	rgGlyGlyGl	uIleGluGly	PheArgheuS	erAlaHisCy	sSerCysAsp	
AGCAGGGATA	ACACACTGCA	AGTGGACATC	AACGGGTTCA	CTACCGGCCG	CCGAGGTGAC	1260
SerArgAspA	snThrLeuGl	nValAspIle	AsnGlyPheT	hrThrGlyAr	GArgGlyAsp	
CTGGCCACCA	TTCATGGCAT	GAACCGGCCT	TTCCTGCTTC	TCATGGCCAC	CCCGCTGGAG	1320
LeuAlaThrI	leHisGlyMe	tAsnArgPro	PheheuLeuL	euMetAlaTh	rProLeuGlu	
AGGGCCCAGC	ATCTGCAAAG	GtgaTCTAGA	CC			1352
ArgAlaGlnH	isLeuGlnSe	r...SerArg				

FIG.2B



**FIG. 3A**



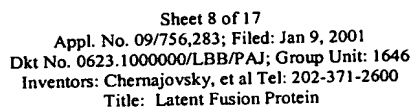
		260	↓280	300
Hu TGF-β	1	-----HGMWRPFLLLMATPLERA-QK--LQSS---RHRRALDTNYCF SST --EKNCV RQLYIDFRKDLG WKWIHEP		
Hu TGF-β	2	KNSGKT---PHLLLMLPSYRL-ESQ----QTNRKKRALDAAYCFRNV--QDNCCLRPLYIDFKRD LGWKWIHEP		
Hu TGF-β	3	QKDNN--N-PHLILMMIPPHRL-DNPQGQQGQ---RKKRALDTNYCFRN L--EENCCVRPLYIDFRQD LGWKWVHEP		
Ck TGF-β	4	-KHRR--V-PYVLAMALPAERANE---LHSA---RRROLDTDYCFGP GTDEKNCCV RPLYIDFRKDLQWKWIHEP		
Fg TGF-β	5	ENT -----KPYL--MITSPAERIDTVT SS---RKRGVGQEYCFGN N-GPNCCVKPLYINFRKDLG WKWIHEP		
		+	+ + + + +	++* + ++ + + +

**FIG. 3B**



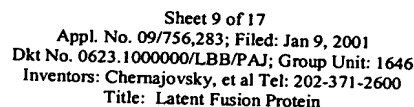
Protein	Sequence	Reference
MMP-1/MMP-8		
Human type I collagen ( $\alpha 1$ )	Ala-Pro-Gln-Gly <sub>775</sub> ~Ile <sub>776</sub> -Ala-Gly-Gln	80
Human type I collagen ( $\alpha 2$ )	Gly-Pro-Gln-Gly <sub>775</sub> ~Leu <sub>776</sub> -Leu-Gly-Ala	80
Human type II collagen	Gly-Pro-Gln-Gly <sub>775</sub> ~Leu <sub>776</sub> -Ala-Gly-Gln	80
Human type III collagen	Gly-Pro-Leu-Gly <sub>775</sub> ~Ile <sub>776</sub> -Ala-Gly-Ile	80
Human $\alpha_2$ -macroglobulin	Gly-Pro-Glu-Gly <sub>679</sub> ~Leu <sub>680</sub> -Arg-Val-Gly	84
Rat $\alpha_2$ -macroglobulin	Ala-Ala-Tyr-His <sub>681</sub> ~Leu <sub>682</sub> -Val-Ser-Gln	84
Rat $\alpha_2$ -macroglobulin	Met-Asp-Ala-Phe <sub>691</sub> ~Leu <sub>692</sub> -Glu-Ser-Ser	84
Rat $\alpha_1$ -macroglobulin	Glu-Pro-Gln-Ala <sub>683</sub> ~Leu <sub>684</sub> -Ala-Met-Ser	84
Rat $\alpha_1$ -macroglobulin	Gln-Ala-Leu-Ala <sub>685</sub> ~Met <sub>686</sub> -Ser-Ala-Ile	84
Chicken ovostatin	Pro-Ser-Tyr-Phe <sub>673</sub> ~Leu <sub>674</sub> -Asn-Ala-Gly	79
Human pregnancy zone protein	Tyr-Glu-Ala-Gly <sub>685</sub> ~Leu <sub>686</sub> -Gly-Val-Val	84
Human pregnancy zone protein	Ala-Gly-Leu-Gly <sub>687</sub> ~Val <sub>688</sub> -Val-Glu-Arg	84
Human pregnancy zone protein	Ala-Gly-Leu-Gly <sub>757</sub> ~Ile <sub>758</sub> -Ser-Ser-Thr	84
$\alpha_1$ -protease inhibitor	Gly-Ala-Met-Phe <sub>352</sub> ~Leu <sub>353</sub> -Glu-Ala-Ile	85
Human aggrecan	Ile-Pro-Glu-Asn <sub>341</sub> ~Phe <sub>342</sub> -Phe-Gly-Val	86
Human aggrecan	Thr-Glu-Gly-Glu <sub>373</sub> ~Ala <sub>374</sub> -Arg-Gly-Ser	86
Human cartilage link	Arg-Ala-Ile-His <sub>16</sub> ~Ile <sub>17</sub> -Gln-Ala-Glu	87
Human insulin-like growth factor binding protein-3	Leu-Arg-Ala-Tyr <sub>99</sub> ~Leu <sub>100</sub> -Leu-Pro-Ala	88

FIG.4A



Source	Sequence	Position
Guinea pig $\alpha 1$ (I) gelatin	Gly-Ala-Hyp-Gly	24
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Gln-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ala-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ser-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ala-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Ala-Lys-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ala-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ala-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Ile-Gly	30
Rat $\alpha 1$ (I) gelatin	Gly-Pro-Hyl-Gly	30
Bovine type 1 collagen ( $\alpha 1$ )	Gly-Pro-Gln-Gly	22
Bovine type 1 collagen ( $\alpha 2$ )	Gly-Pro-Gln-Gly	22
Human aggrecan	Ile-Pro-Glu-Asn	89
Human galectin-3	Pro-Pro-Gly-Ala	90
Human cartilage link	Arg-Ala-Ile-His	87
Human cartilage link	Gly-Pro-His-Leu	87
Human insulin-like growth factor binding protein-3	Leu-Arg-Ala-Tyr	88





**FIG. 4C**



MMP-7			
Human aggrecan	Ile-Pro-Glu-Asn <sub>341</sub> ~Phe <sub>342</sub> -Phe-Gly-Val	89	
Human cartilage link	Gly-Pro-His-Leu <sub>25</sub> ~Leu <sub>26</sub> -Val-Glu-Ala	87	
Human prourokinase	Pro-Pro-Glu-Glu <sub>143</sub> ~Leu <sub>144</sub> -Lys-Phe-Gln	98	
MMP-9			
Human type V collagen ( $\alpha$ 1)	Gly-Pro-Pro-Gly <sub>439</sub> ~Val <sub>440</sub> -Val-Gly-Pro	99	
Human type V collagen ( $\alpha$ 2)	Gly-Pro-Pro-Gly <sub>445</sub> ~Leu <sub>446</sub> -Arg-Gly-Glu	99	
Human type XI collagen ( $\alpha$ 1)	Gly-Pro-Gly-Gly <sub>439</sub> ~Val <sub>440</sub> -Val-Gly-Pro	99	
Human aggrecan	Ile-Pro-Glu-Asn <sub>341</sub> ~Phe <sub>342</sub> -Phe-Gly-Val	89	
Human galectin-3	Pro-Pro-Gly-Ala <sub>62</sub> ~Tyr <sub>63</sub> -His-Gly-Ala	90	
Human cartilage link	Arg-Ala-Ile-His <sub>16</sub> ~Tle <sub>17</sub> -Gln-Ala-Glu	87	
MMP-10			
Human cartilage link	Arg-Ala-Ile-His <sub>16</sub> ~Ile <sub>17</sub> -Gln-Ala-Glu	87	
Human cartilage link	Gly-Pro-His-Leu <sub>25</sub> ~Leu <sub>26</sub> -Val-Glu-Ala	87	

FIG.4D

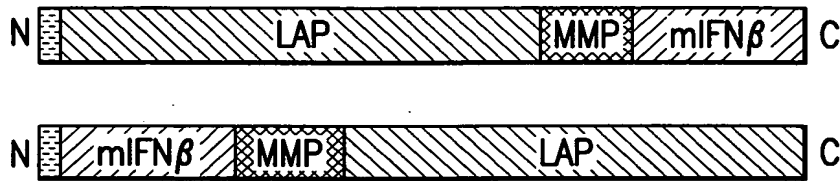


FIG.5A

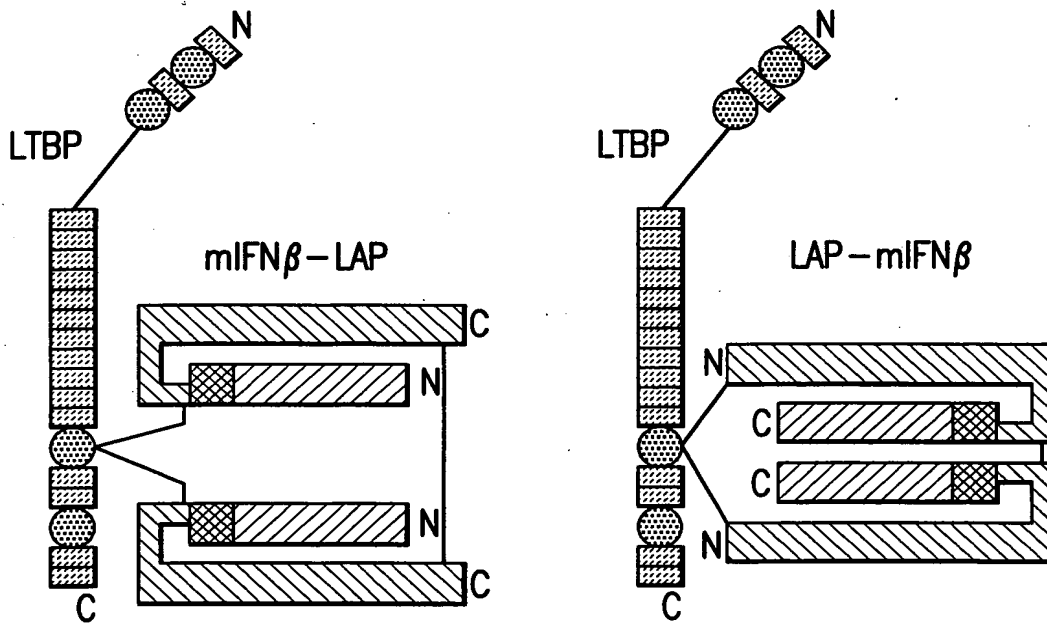
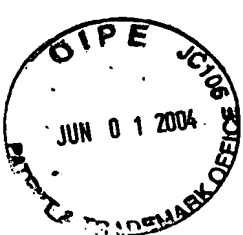


FIG.5B



Sheet 12 of 17  
Appl. No. 09/756,283; Filed: Jan 9, 2001  
Dkt No. 0623.1000000/LBB/PAJ; Group Unit: 1646  
Inventors: Chernajovsky, et al Tel: 202-371-2600  
Title: Latent Fusion Protein

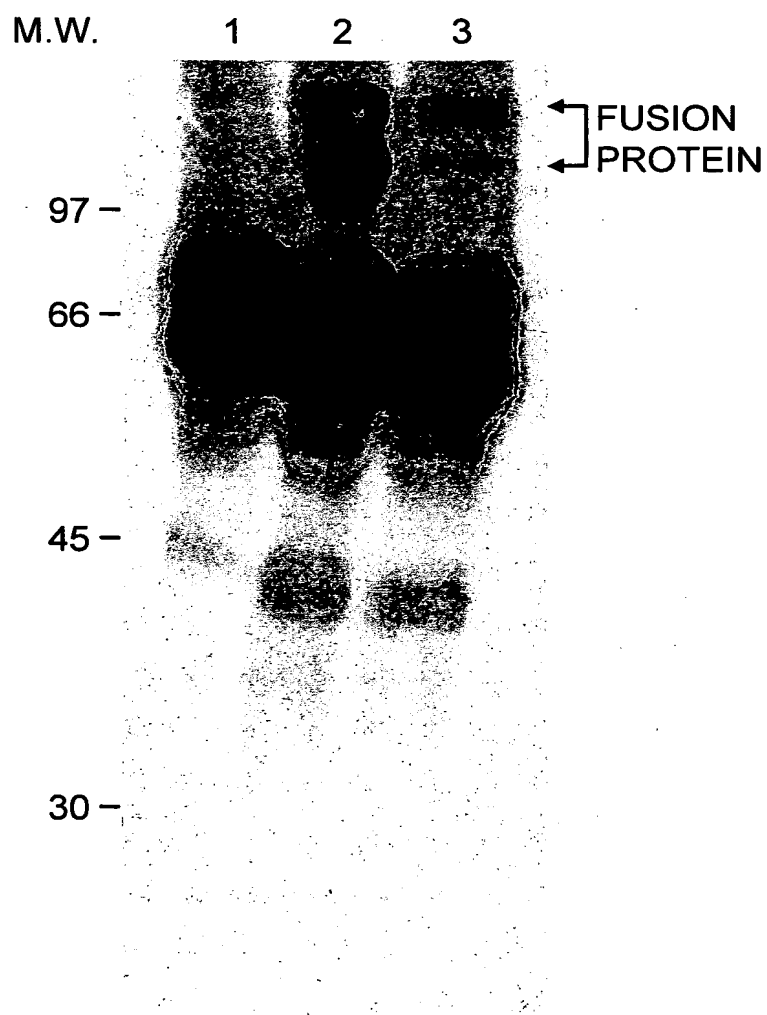


FIG.6

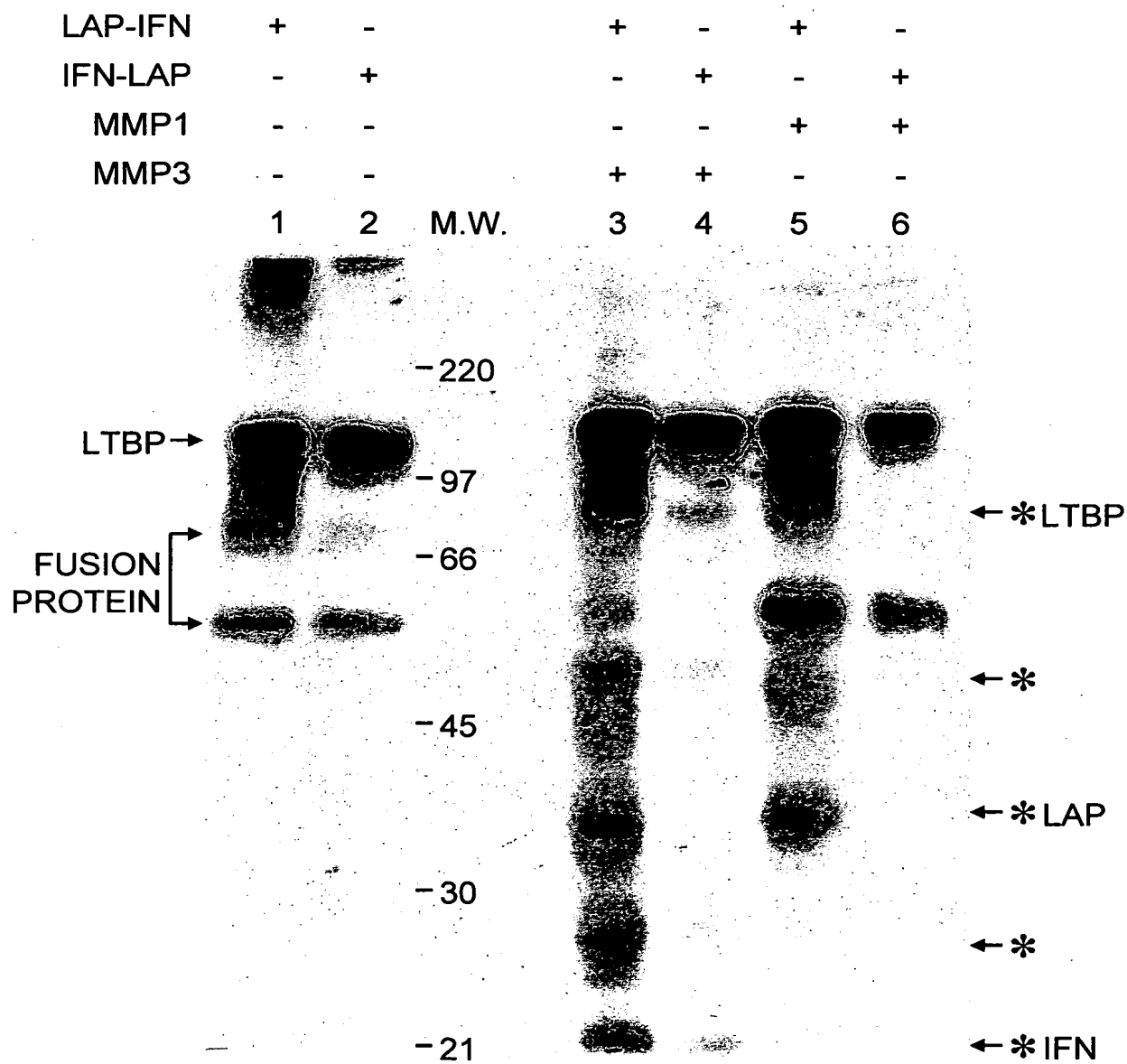


FIG.7

Anti-LAP	+	+	+	+	-	-	-	-
Anti-IFN	-	-	-	-	+	+	+	+
MMP1	-	+	-	-	-	+	-	-
MMP3	-	-	+	-	-	-	+	-
SF	-	-	-	+	-	-	-	+
M.W.	1	2	3	4	5	6	7	8

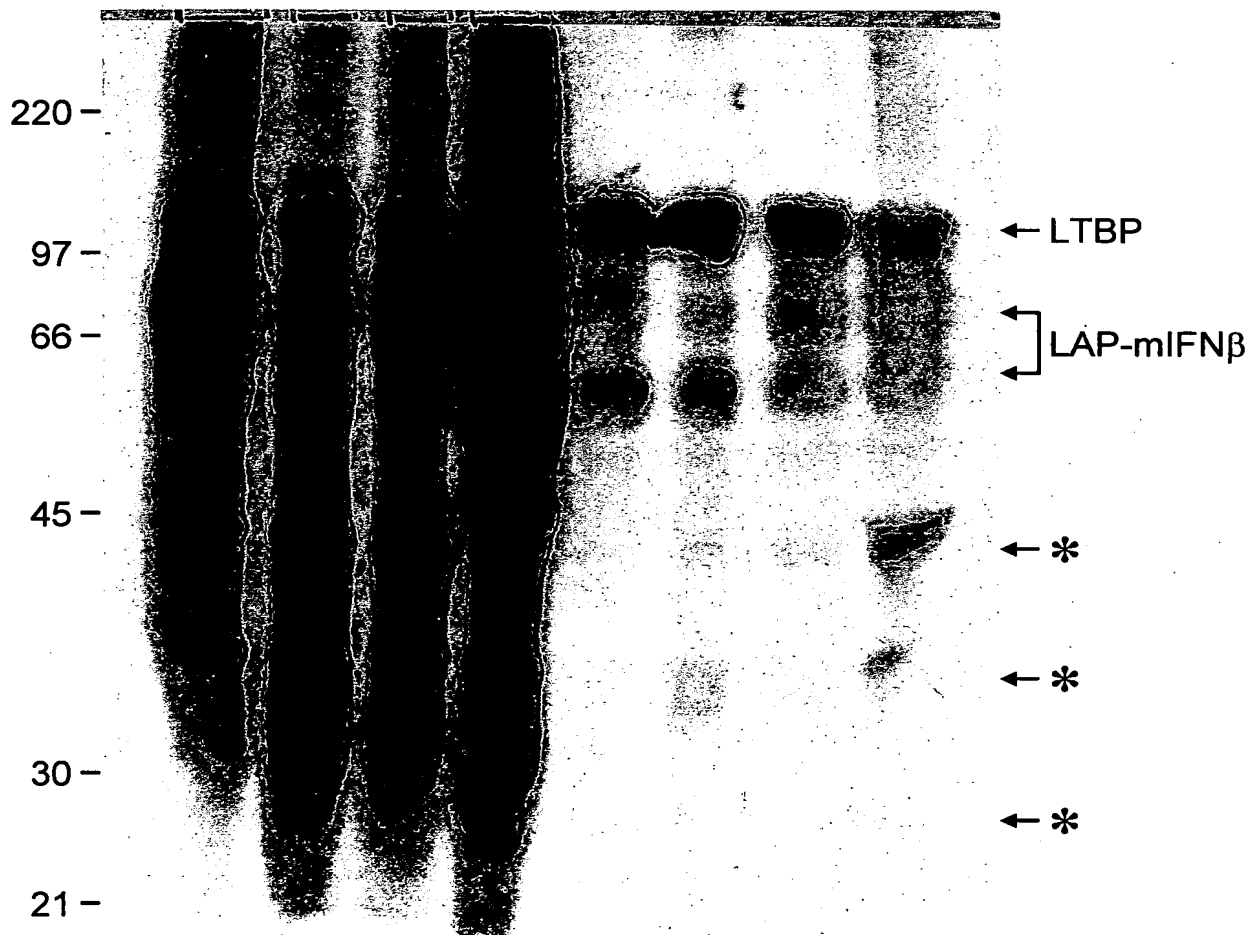


FIG.8A



Anti-LAP	+	+	+	+	-	-	-	-
Anti-IFN	-	-	-	-	+	+	+	+
MMP1	-	+	-	-	-	+	-	-
MMP3	-	-	+	-	-	-	+	-
SF	-	-	-	+	-	-	-	+
M.W.	1	2	3	4	5	6	7	8

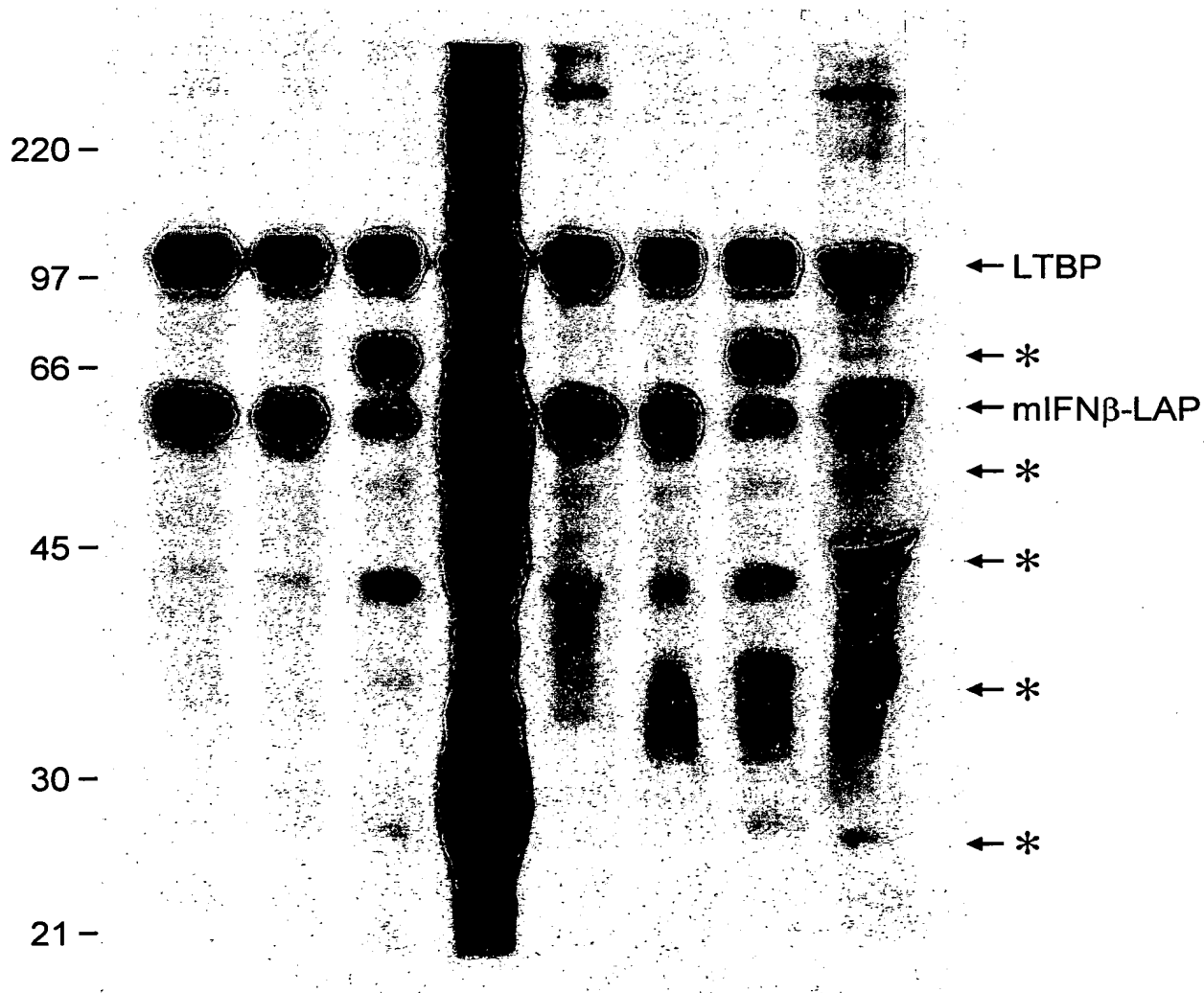


FIG.8B

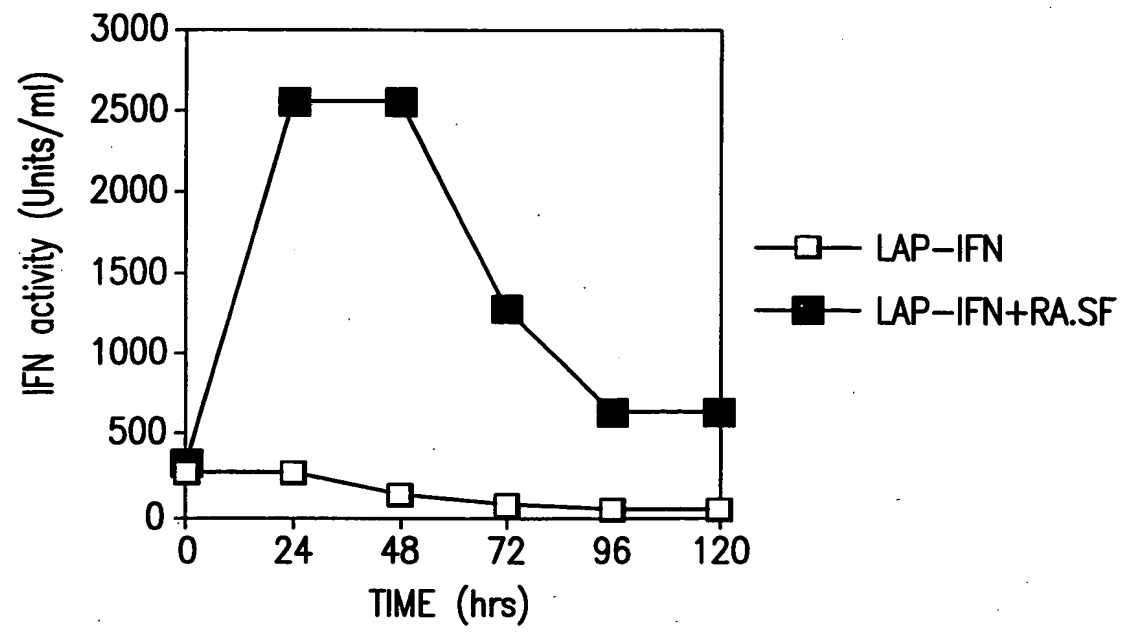


FIG. 9A

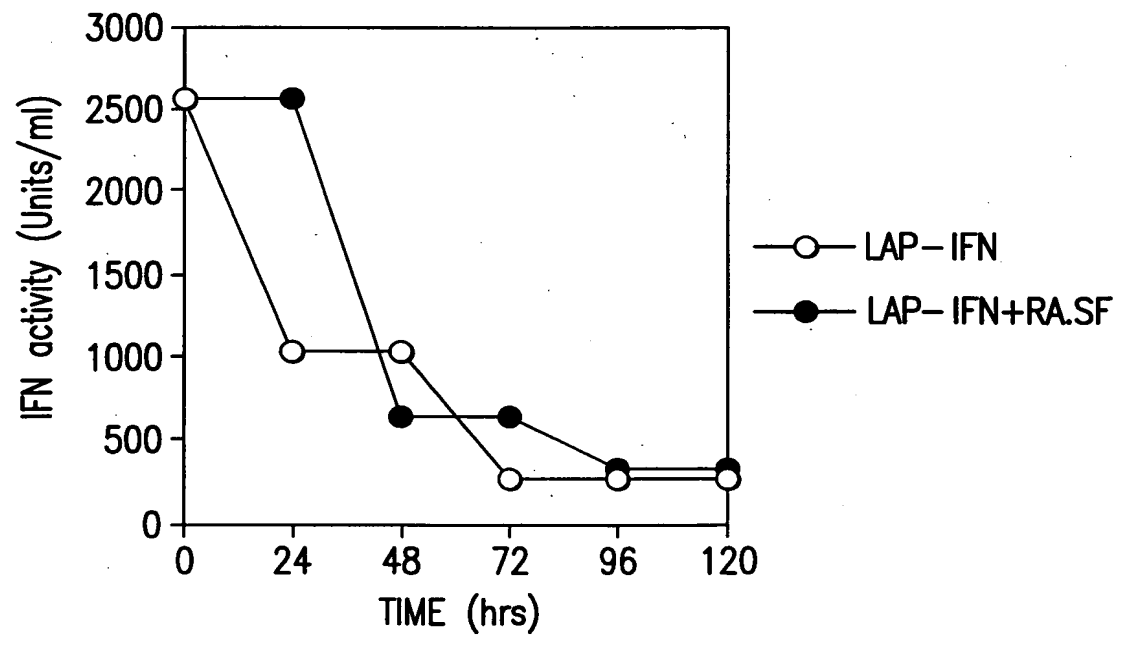
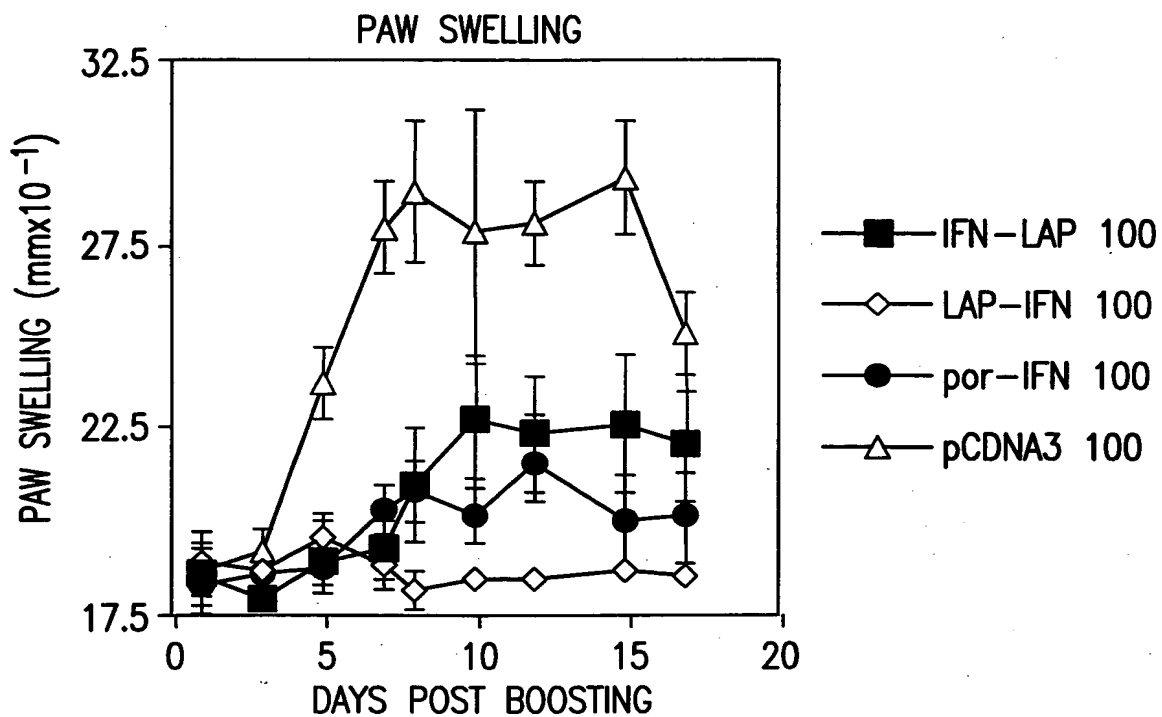
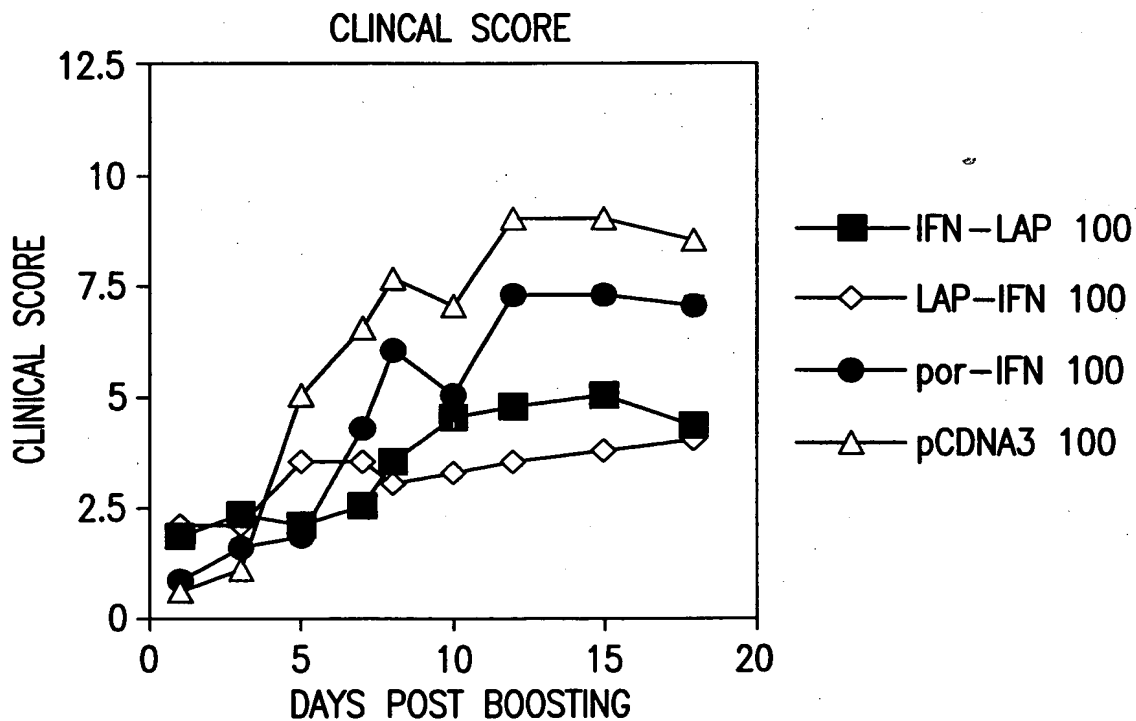


FIG. 9B





**FIG.10A**



**FIG.10B**